

## REMARKS

### **I. Status of the Claims**

Claims 1-84 were originally filed. As the result of a restriction requirement, claims 1-4, 10, 50, and 55 are elected, whereas the remaining claims are withdrawn from consideration. Upon entry of the present amendment, claims 1, 11, 21, 33, 46, and 47 are amended to recite "a heterologous peptide linker" in place of the original term "a peptide linker." This amendment finds support in the specification, *e.g.*, on page 8, line 12. Thus, no new matter is introduced.

### **II. Amendment to the Specification**

The specification is amended to indicate that this application is the national stage of PCT/US02/07144. No new matter is introduced.

### **III. Restriction Requirement**

In the Office Action mailed February 22, 2007, the Examiner maintains and makes final the restriction requirement of October 18, 2006, contending that the restriction requirement is proper because there lacks a single general inventive concept under PCT Rule 13. Specifically, the Examiner argues that a composition having the common technical feature of the claimed invention, a fusion polypeptide of gp120 and gp41 covalently linked by a peptide linker of at least 5 amino acids, has been previously disclosed in Wyatt (US 2004/0109887). Applicants cannot agree, because Wyatt does not teach the use of any linker between gp120 and gp41; rather, the publication describes a cleavage-deficient gp160 $\Delta$ CT, which contains in its protease cleavage site between gp120 and gp41 two point mutations (replacing the two Arg residues with two Ser residues at positions 508 and 511). These two mutations cannot constitute "a peptide linker of at least 5 amino acids," as required by the pending claims.

Although no amendment is necessary, Applicants have hereby amended the pending claims to further distinguish the claimed invention of this application from Wyatt. The amended claims recite that the peptide linker covalently linking gp120 and gp41 is a

"heterologous" peptide linker. The word "heterologous" is defined in paragraph 45 on page 11 of the specification as follows:

The term "heterologous" when used with reference to portions of a nucleic acid indicates that the nucleic acid comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences from unrelated genes arranged to make a new functional nucleic acid, e.g., a promoter from one source and a coding region from another source. Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature (e.g., a fusion protein).

This definition makes it clear that a "heterologous peptide linker," as used in the pending claims, has an amino acid sequence that is (1) at least 5 amino acids in length; and (2) not found in nature as being connected with or a part of the gp160, gp120, and gp41 amino acid sequences. In other words, the amino acid sequence of a heterologous peptide linker is unrelated to gp160, gp120, or gp41 sequence. The two Arg → Ser point mutations with or without their surrounding sequences in gp160 $\Delta$ CT simply cannot be construed as a linker sequence of at least 5 amino acids and also unrelated to gp160, gp120, or gp41.

As such, Applicants contend that Wyatt fails to destroy the single common inventive concept of the present invention: a fusion polypeptide between gp120 and gp41 by a heterologous peptide linker of at least 5 amino acids linking the C-terminal end of gp120 to the N-terminal end of gp41. Accordingly, Applicants strongly urge the Examiner to withdraw of the restriction requirement and examine all pending claims together.

#### **IV. Claim Rejections**

##### 35 U.S.C. §103

Claims 1-3, 10, 50, and 55 are rejected under 35 U.S.C. §103(a) for alleged obviousness over Wyatt (US2004/0109887) in view of Rovinski (U.S. Patent No. 5,866,320). Claims 1-4, 10, 50, and 55 are also rejected under 35 U.S.C. §103(a) for alleged obviousness over Wyatt in view of Root (US2003/0082525). Applicants respectfully traverse the rejections.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143.

As discussed above, Wyatt describes a gp160 $\Delta$ CT containing two Arg  $\rightarrow$  Ser mutations but does not describe or suggest the use of any linker between gp120 and gp41, particularly any linker having the features specified in the pending claims. The two secondary references, Rovinski and Root, are apparently cited for the purpose of providing the limitation of a peptide linker: Rovinski teaches the use of a peptide linker containing a heterologous antigenic epitope in a recombinant non-infectious retrovirus-like particle so as to allow the distinction of this recombinant particle from other retroviruses; Root teaches the construction of a 5-helix protein using a peptide linker containing the GGS GG sequence. Applicants contend that no *prima facie* obviousness is established, at least for the reason that the Examiner has not identified in the cited references any motivation or suggestion to combine the claim limitations.

Wyatt teaches substitution of the two Arg residues within the protease cleavage site so that the resulting gp160 $\Delta$ CT cannot undergo proteolysis at this site. While making the obviousness rejections, the Examiner asserts that placing a peptide linker, such as one described by Rovinski *et al.*, between gp120 and gp41 is motivated by an artisan's desire "to differentiate between infection by HIV or another retrovirus such as non-infectious, retrovirus-like particle" (see page 4 of the Office Action mailed February 22, 2007). The advantage of a Rovinski's linker in having a distinct antigenic epitope is, however, irrelevant to this invention, because a peptide linker is used in this invention to provide a flexible tether between gp120 and gp41, not an identifying marker. Thus, the Examiner has identified no motivation in Wyatt or Rovinski to combine the teaching of the two references.

The Examiner also contends that the motivation to use a linker such as one described by Root *et al.* exists because an artisan would want to "increase the flexibility of the linker" and to "preserve and ... stabilize the native conformation of the gp120-gp41 complex"

(see page 5 of the Office Action). Yet, these alleged motivations find no specific basis in the teaching of the cited references when viewed together. Nowhere in Wyatt have the authors mentioned any reason that might prompt one to consider the strategy of inserting a peptide linker to disrupt the protease cleavage site as an alternative to the point mutations in gp160 $\Delta$ CT. Nor has the Examiner pointed out where in Wyatt can one find any discussion regarding the importance of linker flexibility and preservation of gp120-gp41 conformation. The Root *et al.* reference clearly provides no such specific suggestions either.

It is well settled in the prevailing case law that the obviousness determination must be made when the claimed invention is considered as a whole, the references are considered as a whole, and the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. See, *e.g.*, *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187n5 (Fed. Cir. 1986), and MPEP §2141 II. Applicants contend that, since the generalized advantages of using a peptide linker between gp120 and gp41 as alleged by the Examiner find no specific basis in the cited references, these advantages are nothing more than a motivation or suggestion that became apparent only in the hindsight afforded by the present invention. Such alleged advantages thus cannot be relied on as the motivation or suggestion necessary for establishing a *prima facie* case of obviousness.

As such, Applicants respectfully request that the obviousness rejections under 35 U.S.C. §103(a) be withdrawn.

Appl. No. 10/506,651  
Amdt. dated April 16, 2007  
Reply to Office Action of February 22, 2007

PATENT

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Chuan Gao', with a stylized, flowing script.

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